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## The Calophyllum story

### The *Calophyllum* story

The story of *Calophyllum* is an exciting one for the Forest Department of Sarawak from the viewpoint of phytochemical survey in the State. *Calophyllum* or Bintangor as it is called locally, is a genus of the family Guttiferae to which the popular local fruit, Buah manggis or mangosteen, also belongs. It started in December 1986 when the Arnold Arboretum of the Harvard University in Massachusetts, U.S.A requested the permission of the State Government of Sarawak to collaborate with the Forest Research Division of the Forest Department on a field collection of Sarawak plants for phytochemical analyses. The Arnold Arboretum was at that time contracted by the University of Illinois at Chicago which had been awarded a grant by the National Cancer Institute U.S.A. to "co-ordinate the collection of selected plant specimens from the forests of tropical Asia in order to screen for tumour-arresting properties". The mission of the National Cancer Institute (NCI) is to find new drugs for cancer and AIDS. Permission was given for the collaboration by the State Government in May 1987.

Collection of plant specimens commenced in September 1987 when Dr John Burley, a Research Associate from the Arnold Arboretum joined force with Bernard Lee (then a Forest Officer) and other officers from the Herbarium of the Department on a plant specimen collection trip. The plant specimen collection was carried out in a lowland mixed dipterocarp forest near Bintulu, an alluvial forest near the Gunung Mulu National Park, a submontane forest in the Matang area near Kuching, the limestone hills near Bau and a peatswamp and a kerangas forest near Lundu.

Emphasis during collection was placed on :

1. flowering plants
2. species from as wide a variety of families and genera as possible
3. plants reputed to have medicinal uses locally.

The initial plant collecting operation was to procure 0.5 - 1.0 kg dry weight of samples so as to evaluate the promise of each species through screening procedures for anticancer activity.

The list of genera and species extensively screened by the NCI was used as a guide. Genera and species, which had been previously screened, were given a low priority during collection. Ten duplicates of each herbarium specimens were collected. In all 476 samples from 131 species were collected including 67 from the Lundu area. The samples from Lundu included two of *Calophyllum* in the peatswamp forest near Batang Kayan 3-5 km south of Lundu. These two samples were identified as sample Burley 341 and 351. Tree bark, twigs, flowers and leaves were collected from the species.

All samples were tested for tumour-arresting properties but were found to be negative. As a routine, the same samples were subjected to tests against HIV. The breakthrough came in late 1991 when the Forest Department of Sarawak was informed by the NCI that an extract from sample Burley 351 exhibited positive activity against the HIV.

Sample Burley 351 was identified as *Calophyllum lanigerum* var. *austrororiaceum*. The active compound was identified as Calanolide A, a coumarin. As a result of this development, efforts were made to collect more samples of the plant for further testing. In March 1992, Dr. D. D. Soejarto from the College of Pharmacy of the University of Illinois at Chicago came to Sarawak and accompanied by officers of the Sarawak Herbarium, proceeded to the previous collection site to try and recollect the samples. It was at this time that Sarawak received a lot of bad publicity in the press because the original tree from which the earlier samples were collected could no longer be located. There were claims in the press, particularly those in Singapore, that the 'tree of life' had been logged. The Forest Herbarium staff later established that the area in which the tree was found could not have been logged because it is a dilapidated peatswamp forest area with no commercial value. The tree, it was established after interviews with the original field collection crew, had in fact been felled during sample collection as it was only a small tree. It was also clear that logging had not taken place in the sample collection area. In any case further samples of the same species were collected. Out of the six samples then recollected, only one tested positive but chemical verification indicated that the compound found here was not the same as that found in the previous active tree collected by John Burley and Bernard Lee's party. Further samples of the same species collected elsewhere viz. the Bako National Park and the Singapore Botanic Garden also tested negative. In June 1992, Calanolide A extracted from *Calophyllum lanigerum* was approved by a Decision Network Meeting at the NCI for drug development.

During the field trip to recollect samples of *Calophyllum lanigerum* var. *austrororiaceum*, samples from another species, *C. teysmannii* var. *inophylloide* were collected from logged over areas in the Sampadi Forest Reserve near Lundu and brought to the NCI for testing. Subsequent analyses revealed the species to yield another compound, Costatolide, which also exhibits positive reaction against the HIV.

In August 1992 a draft of a Memorandum of Understanding between the Developmental Therapeutics Program of the NCI and the Department of Forestry Sarawak was presented to the Department. The memorandum set out the terms of collaboration between the two parties for the collection and supply of plant materials for screening on the part of the Department on the one hand and the screening, fractionation, structural elucidation and isolation of active compounds from the materials supplied by NCI on the other. The State Government was not in entire agreement with the terms of the collaboration especially clauses relating to the ownership of patents, the payment of royalties and other financial benefits from the use of the biological resource from the State for drug development and the right to the issue of licences for the subsequent manufacture of drugs in the event of a successful development. In May 1993, the State Attorney-General, Datuk J.C.Fong and Dr. Lee Hua Seng (then Assistant Director of Research in the Forest Department of Sarawak) were invited by the NCI to visit its facilities and to further negotiate with legal personnel of the NCI the terms of the collaboration. The terms of the MOU cover aspects on (a) co-inventorship (b) financial benefits from the use of the State's biological resource for drug development and (c) the obligation of NCI to assist the State in the development of local capability to undertake the isolation, screening, fractionation, structural elucidation of active compounds from plants and marine organisms. The MOU also provides for the payment of royalties in the event of a drug being synthesised from the compound developed from the natural products. The Memorandum of Understanding was finalised in the middle of 1994 and the State Government represented by the State Secretary, Tan Sri Datuk Amar Haji Hamid Bugo and the National Cancer Institute represented by the Head of the Natural Products Division, Dr Gordon M.Cragg put their signatures on the document on 21 June 1994 in the presence of the Chief Minister of Sarawak.

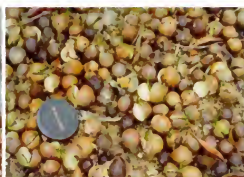
It was during the visit to the NCI by the State Attorney-General and Dr. Lee Hua Seng, on 24 May 1993, in another Decision Network Meeting, that Costatolide was approved as an interim replacement for Calanolide for preclinical testing. The difficulty with Calanolide has been that although it is more potent than Costatolide, the yield from the raw materials is very low, approximately 0.05% and the compound can only be extracted from the twigs and leaves. Costatolide, on the other hand, is extracted from the latex of the trees of *C. teysmannii* and the yield of the compound from the raw material is very much higher, between 20-25%. The availability of the compound from the latex means that the trees need not be felled in the process of sample collection which is the case with *C. lanigerum*. The latex can be tapped and the trees can thus be conserved for the continuous supply of raw materials. The research collaboration has reached a stage where the NCI had requested the supply of a substantial amount of the latex of *C. teysmannii* to advance to clinical trials. This commenced towards the end of 1998.

In June 1993, the State, on the recommendation of the State Attorney-General made an order referred to as **The Calophyllum Species**

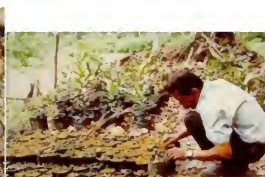
(Prohibition of Felling and Restriction of Export) Order under Section 96(a) and (b) of the Forests Ordinance. The objective of the Order is to ensure that the source of the raw materials of the two Bintangor species is conserved, by the prohibition of felling and the restriction of export of the two *Calophyllum* species without the permission of the Director of Forests, for harvesting in the event of a successful drug development. At the same time as the Order was made, a full survey was launched to determine the abundance and distribution of the two species. In addition trial planting of the two species using wildlings collected in the field was initiated.



Seeds of (*Calophyllum teysmannii* var. *inophylloide*)



Seeds germinating



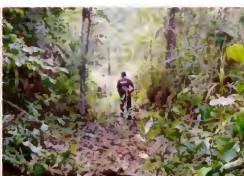
Germinating seeds being potted



Potted Seedlings



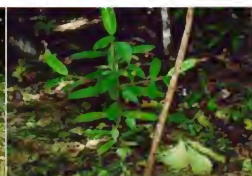
Potted seedlings ready for planting



Planting along cut lines in secondary forest



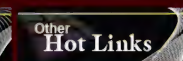
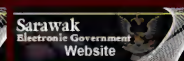
Planted seedlings being maintained



Planted seedlings

The two compounds, Calanolide and Costatolide, were later re-classified as (+)-Calanolide A and (-)-Calanolide B respectively. A joint venture company Sarawak MediChem Pharmaceuticals, Inc. was set up by the Sarawak Government and MediChem Research, Inc. to look into (a) the primary clinical development of (+)-Calanolide A for the treatment of HIV and (b) the secondary development of other compounds displaying anti-viral activities.

In addition the storage properties of the latex of the two species of *Calophyllum* are being investigated in collaboration with College of Pharmacy at the University of Illinois at Chicago, U.S.A.



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